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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
| 09/713,794 | 11/15/2000 | Yannick Batard | A32000-A-072667.0172 | 4605 |
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EXAMINER
LAMBERTSON, DAVID A
ART UNIT 1636 PAPER NUMBER 14

DATE MAILED: 08/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|---------------------|---------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/713,794 | BATARD ET AL. |
| | Examiner | Art Unit |
| | David A. Lambertson | 1636 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 19 June 2003.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-28 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-13,15-18 and 22-27 is/are rejected.

7) Claim(s) 14,19-21 and 28 is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

- Certified copies of the priority documents have been received.
- Certified copies of the priority documents have been received in Application No. 09/158,767.
- Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____

4) Interview Summary (PTO-413) Paper No(s) _____

5) Notice of Informal Patent Application (PTO-152)

6) Other: _____

DETAILED ACTION

Receipt is acknowledged of a Reply and a Terminal Disclaimer, filed June 19, 2003 as Paper Nos. 12 and 13, in response to the previous Office Action. Amendments were made to the claims.

Claims 1-28 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, Paper No. 11, mailed March 25, 2003, that is not addressed in this action has been withdrawn.

The Terminal Disclaimer has been considered and entered, and is in condition to obviate the rejection of Claim 27 under the judicially created statute of obviousness-type double patenting.

Because the rejections set forth in this Office Action are necessitated by amendment, this Office Action is made FINAL.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 7, 8, 11-13, 15-18 and 22-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kotula et al. (cited in the previous Office Action; see entire document; henceforth Kotula) in view of Neill et al. (cited in the previous Office Action; henceforth Neill;

see entire document). **This is a new rejection that is necessitated by amendment of the claims.**

Kotula teaches a method of enhancing the production of a non-yeast protein (mouse IG Kappa gene; henceforth mIGK) by optimizing the codon bias of the mIGK to reflect the codon bias of yeast (see for example the Abstract). This teaching (described in detail below, as it relates to the claimed invention) also presents a general teaching that can be used as a road map for the optimization of non-mIGK genes.

Kotula teaches a recombinant yeast cell comprising a non-yeast DNA (mIGK), wherein the codon bias of the mouse gene is optimized for the enhanced expression of the gene in the yeast *S. cerevisiae* (see for example page 1386, right side, first full paragraph). Overall, 115 of 215 (53%) of the codons were replaced (necessarily indicating that at least one stretch of 10 consecutive codons had at least 2 or more codons replaced), some of which were in the 5' region of the gene, and the expression of the gene was found to increase 5-fold over that of the mouse cDNA sequence without codon optimization (see for example page 1386, right hand side). Since the gene as optimized contains DNA sequences that are not ordinarily part of the gene, the optimized gene is by definition a chimeric gene. The genes were cloned into the backbone of yeast expression vector pBR, which contains regulatory and selection sequences that are operable in yeast (see for example the legend of Figure 1), thereby teaching a yeast expression vector. The mIGK protein was produced in the method of Kotula, therefore Kotula teaches a method of producing the protein with such a yeast cell (see for example Figure 3).

Kotula does not specifically teach the codon optimization of a plant enzyme for production in recombinant yeast. However, Kotula provides a general teaching on the

optimization of codons for increased expression of a heterologous gene in yeast, and it would be obvious to one of ordinary skill in the art to use any known gene sequence in the method of Kotula.

Neill teaches the production of wheat α -gliadin (a plant gene, specifically from wheat) in yeast (see for example the abstract and page 313, section (e)). Neill goes on to suggest that α -gliadin has a potential translation limitation in yeast due to the availability of a particular glutamine tRNA (see the last line of the Abstract), further indicating that codon bias usage maybe a factor in the production of heterologous proteins in yeast (see for example page 313-315, the bridging paragraph). Neill also teaches that the recombinant production of α -gliadin is important as a constituent of doughs (see for example page 304, bridging paragraph for the left and right sides of the page), and that the study of the α -gliadin gene would be greatly aided by the ability to express and manipulate the gene in the heterologous yeast system (see for example page 304, penultimate sentence of the first paragraph).

It would have been obvious to the ordinary skilled artisan to combine the teachings of Kotula with those of Neill to result in the claimed invention because Neill teaches that the overexpression of α -gliadin in yeast is limited by codon availability in yeast (particularly a glutamine tRNA), and Kotula teaches a general method of overcoming the limitations of codon bias in yeast by replacing poorly utilized codons in yeast (such as the aforementioned glutamine tRNA codon) with codons that are more optimally used in yeast. The ordinary skilled artisan would have been motivated to combine the teachings with the expected benefit of increasing the overexpression and therefore production of α -gliadin, which is a valuable wheat protein used as a constituent in doughs, as taught by Neill.

Absent evidence to the contrary and given the teachings of the stated prior art and the high level of skill of the ordinary skilled artisan at the time of the applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 2-6, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kotula in view of Neill as applied to claim 1 (and 7, 8, 11-13, 15-18 and 22-27) in the preceding rejection, in further view of the Codon Usage Database (cited in the previous Office Action; see entire document; henceforth CUD). **This is a new rejection that is necessitated by amendment of the claims.**

Kotula in view of Neill teaches the same elements as set forth above in the rejection of claim 1 (and 7, 8, 11-13, 15-18 and 22-27) under 35 USC §103(a).

Kotula in view of Neill does not teach what specific codons should be used for yeast, nor does it teach the relative frequencies of the codons in yeast.

The CUD teaches the codon bias and relative frequencies (per thousand; e.g. codons having less than 13 copies per 1000 in yeast, such as CTC) for a vast number of organisms, including yeast (see for example the homepage of the aforementioned website, as well as the particular web page for the yeast *S. cerevisiae*). Inspection of the specific yeast page indicates that a codon such as CTC (i.e., CUC) has a very low frequency in yeast (5.4 copies per 1000). Similarly, CTG (CUG), CTT (CUU), and a number of other codons are also shown in the CUD to have very low codon representation in terms of copy number per 1000. Furthermore, the website was present prior to the filing or priority date of the instant specification.

It would have been obvious to the ordinary skilled artisan to combine the teachings of Kotula in view of Neill with those of the CUD to result in the claimed invention because the ordinary skilled artisan would want to be certain they were optimizing the codons to the fullest extent applicable for the particular yeast strain, therefore they would naturally consult the CUD which has accumulated the knowledge of what codons are poorly represented (have a low frequency per 1000) and which codons are better represented (have a higher frequency per 1000). For example, if a plant gene such as α -gliadin (as taught by Neill) was to be expressed in yeast by the method of Kotula (wherein the codons were optimized relative to the abundance of codons in yeast), the ordinary skilled artisan would consult the CUD to determine what codons were poorly represented in yeast (i.e., there were a low number of copies per 1000) in order to determine what codons would need to be optimized. For instance, the ordinary skilled artisan would recognize that a CGG codon (1.7 copies per 1000) or a CGA codon (3.0 copies per 1000) in the α -gliadin gene would need to be replaced with a more abundant codon for arginine (e.g., AGA having 21.3 copies per 1000) because their representation/codon bias was very low and could reduce the production of protein as taught by Kotula. The ordinary skilled artisan would have been motivated to combine the teachings with the expected benefit of knowing for certain that they had appropriately and fully optimized the coding sequence of the desired protein (e.g., for the α -gliadin wheat gene, as taught by Neill) in order to produce a protein as efficiently as possible using the method of Kotula.

Absent evidence to the contrary and given the teachings of the stated prior art and the high level of skill of the ordinary skilled artisan at the time of the applicants' invention, it must

be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Response to Arguments Concerning Rejections Under Claim Rejections - 35 USC § 103

Applicant's arguments are directed to rejections set forth in the previous Office Action and the rejections set forth in the instant Office Action are necessitated by amendment.

However, the references that are applied in the rejections that are necessitated by amendment are the same as those set forth in the rejections indicated in the previous Office Action. Since these references are applied for the same manner, although in a different context as a result of Applicant's amendment of claim 1, Applicant's arguments are addressed below as they relate to the new rejections that have been necessitated by amendment.

Applicant's arguments filed June 19, 2003 have been fully considered but they are not persuasive. Applicant makes the following points as it concerns the use of the CUD as a reference in the rejection of claims 2-6 (for clarity purposes, this argument would most appropriately correspond to the rejection of claims 2-6, 9 and 10 as necessitated by amendment, with the consideration that the amendment necessitated the use of Neill as a secondary reference):

1. The teachings of Kotula do not teach each and every limitation of the claimed invention.

Although Kotula does teach the replacement of certain codons in a mouse gene with those codons that are most frequently used in yeast, they are silent with respect to the use of codons other than those that are most frequently used in yeast.

2. Neither the teachings of the Codon Utilization Database nor the teachings of Kotula provide any classification of the yeast codons into well-suited or poorly suited codons.

Applicant's arguments are not found convincing for the following reasons:

1. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Thus, the fact that Kotula does not teach each and every aspect of the claimed invention is irrelevant in light of the fact that a secondary reference is provided that does teach the limitations.
2. The assertion that the CUD does not provide any classification of yeast codons into well-suited or poorly suited codons is incorrect. In fact, it is the information in the CUD that applicant refers to in the specification as describing what codons are well suited and poorly suited to yeast (see for example page 3). Thus the CUD must provide the classification, or the instant specification is also devoid of such classification.

In conclusion, applicant has not provided a reasonable rationale as to why the combined teachings of Kotula and the CUD do not teach the previously claimed invention. Thus, there is no clear reason as to why the references cannot be applied to the instant claims, with respect to the amendments in the claims.

Applicant's arguments filed June 19, 2003 have been fully considered but they are not persuasive. Applicant makes the following points as it concerns the rejection of claims 15-18:

1. The teachings of Kotula do not teach each and every limitation of the claimed invention. Kotula is silent with respect the expression of plant genes in yeasts.
2. The teachings of Neill provide several potential reasons for the poor production of a plant gene in yeasts. Although these reasons include codon usage bias, Neill does not specifically teach that codon usage bias is the critical reason for this poor production of a plant gene in yeasts. Furthermore, Neill in fact provides a solution, which involves the overproduction of a poorly represented codon in yeast, to overcome the deficiencies in the production of the plant gene in the yeast.

Applicant's arguments are not found convincing for the following reasons:

1. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Thus, the fact that Kotula does not teach each and every aspect of the claimed invention is irrelevant in light of the fact that a secondary reference is provided that does teach the limitations.
2. In response to applicant's argument that Neill also suggests that there are other potential solutions to alleviate the poor production of α -gliadin in yeast, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). The fact of the matter is that Neill indicates a problem with codon bias usage as it regards the production of the plant

gene α -gliadin in yeast, namely the yeast is deficient in a particular codon needed in high abundance for the production of α -gliadin. Kotula offers a solution as it regards manipulating the codon usage of a gene to be produced, and the ordinary skilled artisan would recognize that combining the teachings of Kotula with the teachings of Neill would result in an amelioration of the codon bias problem for expressing α -gliadin in yeast.

In conclusion, applicant has not provided a reasonable expectation as to why the combined teachings of Kotula and Neill do not teach the previously claimed invention. Thus, there is no clear reason as to why the references cannot be applied to the instant claims, with respect to the amendments in the claims.

Allowable Subject Matter

Claims 14, 19-21 and 28 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
August 18, 2003


DAVID GUZO
PRIMARY EXAMINER